The COMPASS Trial: Net Clinical Benefit of Low-Dose Rivaroxaban Plus Aspirin as Compared With Aspirin in Patients With Chronic Vascular Disease

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Abstract: BACKGROUND Rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid (aspirin; ASA) 100 mg reduced the risk of cardiovascular events as compared with ASA monotherapy in the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) but increased the risk of major bleedings. Analysis of net clinical benefit (NCB) is of key clinical relevance and represents an integrated measure of overall patient outcome. METHODS The current prespecified analysis was performed to assess the NCB of adding rivaroxaban 2.5 mg twice daily to ASA monotherapy in patients with chronic vascular disease in the COMPASS study cohort (intention-to-treat study population), with a specific focus on high-risk subgroups. The predefined NCB outcome was the composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ. RESULTS A lower number of NCB adverse outcomes was observed with rivaroxaban 2.5 mg twice daily plus ASA versus ASA alone (hazard ratio, 0.80 [95% CI, 0.70-0.91], P=0.0005), which became increasingly favorable with longer treatment duration. The main drivers of NCB outcomes were "efficacy" events, in particular stroke (0.5%/y versus 0.8%/y; hazard ratio, 0.58 [95% CI, 0.44-0.76], P<0.0001) and cardiovascular death (0.9%/y versus 1.2%/y; hazard ratio, 0.78 [95% CI, 0.64-0.96], P=0.02), whereas the bleeding components of the NCB, in particular fatal bleeding (0.09%/y versus 0.06%/y; hazard ratio, 1.49 [95% CI 0.67-3.33], P=0.32), only represented a minority of NCB events. In selected high-risk subgroups, including patients with polyvascular disease (2 vascular beds affected with atherosclerosis), impaired renal function, heart failure, and/or diabetes mellitus, a larger absolute risk reduction for experiencing a NCB event was observed. CONCLUSIONS Compared with ASA monotherapy, the combination of rivaroxaban 2.5 mg twice daily plus ASA resulted in fewer NCB events primarily by preventing adverse efficacy events, particularly stroke and cardiovascular mortality, whereas severe bleedings were less frequent and with less clinical impact. The NCB was particularly favorable in high-risk subgroups and those with multiple risk characteristics. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01776424.

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ORIGINAL RESEARCH ARTICLE

The COMPASS Trial

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METHODS: The current prespecified analysis was performed to assess the NCB of adding rivaroxaban 2.5 mg twice daily to ASA monotherapy in patients with chronic vascular disease in the COMPASS study cohort (intention-to-treat study population), with a specific focus on high-risk subgroups. The predefined NCB outcome was the composite of cardiovascular death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into a critical organ.

RESULTS: A lower number of NCB adverse outcomes was observed with rivaroxaban 2.5 mg twice daily plus ASA versus ASA alone (hazard ratio, 0.80 [95% CI, 0.70–0.91], *P*=0.0005), which became increasingly favorable with longer treatment duration. The main drivers of NCB outcomes were "efficacy" events, in particular stroke (0.5%/y versus 0.8%/y; hazard ratio, 0.58 [95% CI, 0.44–0.76], *P*<0.0001) and cardiovascular death (0.9%/y versus 1.2%/y; hazard ratio, 0.78 [95% CI, 0.64–0.96], *P*=0.02), whereas the bleeding components of the NCB, in particular fatal bleeding (0.09%/y versus 0.06%/y; hazard ratio, 1.49 [95% CI 0.67–3.33], *P*=0.32), only represented a minority of NCB events. In selected high-risk subgroups, including patients with polyvascular disease (≥2 vascular beds affected with atherosclerosis), impaired renal function, heart failure, and/or diabetes mellitus, a larger absolute risk reduction for experiencing a NCB event was observed.

CONCLUSIONS: Compared with ASA monotherapy, the combination of rivaroxaban 2.5 mg twice daily plus ASA resulted in fewer NCB events primarily by preventing adverse efficacy events, particularly stroke and cardiovascular mortality, whereas severe bleedings were less frequent and with less clinical impact. The NCB was particularly favorable in high-risk subgroups and those with multiple risk characteristics.

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Clinical Perspective

What Is New?

- Compared with acetylsalicylic acid (aspirin) monotherapy, the combination of rivaroxaban 2.5 mg twice daily plus aspirin resulted in fewer net clinical benefit events primarily by preventing adverse efficacy events, particularly stroke and cardiovascular mortality, whereas severe bleedings were less frequent and had less clinical impact.
- The net clinical benefit was particularly favorable in high-risk subgroups and those with multiple risk characteristics.

What Are the Clinical Implications?

- "Net clinical benefit" represents an easy to use integrative measure of overall patient benefit in daily clinical practice by combining efficacy and safety outcomes of important clinical relevance (ie, myocardial infarction, stroke, cardiovascular death, life-threatening and fatal bleedings).
- Use of the predefined net clinical benefit of adding rivaroxaban 2.5 mg twice daily to aspirin demonstrates fewer serious adverse events.
- Our data may hence help clinicians and patients in their shared decision-making process of choosing the optimal antithrombotic therapy.
- This is particularly true for high-risk patients, who are frequently undertreated because of the fear of severe bleeding events.

Patients with chronic coronary syndromes or peripheral artery disease (PAD) remain at an increased risk of cardiovascular events over the long term.[1] The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) demonstrated that in patients with chronic coronary syndromes and/or PAD, the combination of rivaroxaban 2.5 mg twice daily plus acetylsalicylic acid (aspirin) (ASA) 100 mg reduced the risk of cardiovascular events as compared with ASA monotherapy, albeit at an increased risk of major bleeding.[2] Rivaroxaban 5 mg twice daily versus ASA did not significantly reduce the primary outcome.

In clinical practice it may be difficult to weigh a reduction in ischemic events against an increase in bleeding events. For such practical purposes, the net clinical benefit (NCB) may constitute a better representation of the "net clinical value" of a novel treatment strategy, incorporating the most severe efficacy and safety events into 1 metric. By doing so, the NCB represents a more comprehensive measure of overall patient outcome rather than separately focusing on single events such as myocardial infarction (MI), stroke, or major bleeding. Indeed, patients with chronic vascular disease are frequently at risk of both severe ischemic and bleeding events, which both need to be taken into account to evaluate the value of an additional antithrombotic therapy.

The current prespecified analysis was therefore performed to assess the NCB of the combination of rivaroxaban 2.5 mg twice daily plus ASA versus ASA monotherapy in patients with chronic vascular disease in the overall COMPASS study cohort and in selected high-risk subgroups.

METHODS

Trial Design and End Points

The design and primary outcomes of the COMPASS trial have previously been published.[2,3] Requests for data access will be considered by the COMPASS Publications Committee on an individual basis beginning 4 years after publication of the main results.[2] In brief, COMPASS was a double-blind, multicenter, randomized clinical trial that enrolled 27 395 high-risk patients with a clinical history of coronary and/or PAD, comparing ASA alone (with rivaroxaban placebo) to the combination of rivaroxaban 2.5 mg twice daily and ASA, or rivaroxaban 5 mg twice daily (with ASA placebo). The study was approved by an institutional review board at each site, and all participants gave informed consent before study procedures. The antithrombotic comparisons in the trial were stopped early after a mean follow-up of 23 months because of clear benefit of rivaroxaban 2.5 mg twice daily plus ASA over ASA alone; we therefore limited our current analysis to this trial population (n = 18 278).

The primary efficacy outcome of COMPASS was a combination of cardiovascular death, stroke, or MI; the principal safety end point was major bleeding according to modified International Society on Thrombosis and Haemostasis (ISTH) criteria, including fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay). The predefined NCB outcome, based on previous anticoagulation trials,[4,5] was the composite of cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ (including intraarticular, intramuscular with compartment syndrome, intraspinal, intracranial, intraocular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or bleeding into the surgical site requiring reoperation).[2]

NCB Analysis

We analyzed the occurrence of NCB events in the overall study cohort and in previously identified high-risk subgroups of the COMPASS population, including patients with polyvascular disease (≥2 vascular beds affected with atherosclerosis), impaired renal function (estimated glomerular filtration rate ≤60 mL/min), heart failure, diabetes mellitus, or a combination of these risk characteristics.[5] We also analyzed the NCB in patients <65 years of age (in such patients the study mandated for the presence of additional risk factors) and ≥65 years of age.[6,7]

Statistical Analysis

All analyses were conducted in the intention-to-treat study population. Baseline characteristics are presented as mean±SD for continuous variables and frequencies for categorical variables. Baseline characteristics were compared with the Wilcoxon rank sum tests for continuous variables and $\chi 2$ tests for categorical variables. Survival analyses were based on the time to a first event. Event rates were expressed per 100 patient-years of follow-up. Stratified Cox proportional hazards regression models were used to estimate hazard ratios (HR) and corresponding 95% CIs to compare the effects of rivaroxaban plus ASA versus ASA alone in selected high-risk subgroups. Significance was tested using stratified log-rank tests. The assumption of the proportional hazards was verified using the plots of log of the negative log of survival function against the log of time. Absolute risk reduction (ARR) was calculated as the difference between Kaplan-Meier cumulative risks of an outcome in rivaroxaban 2.5 mg twice daily plus ASA and ASA alone treatment groups at 12, 24, and 30 months of follow-up. ARR is expressed as events prevented/caused per 1000 patients treated. There was no correction for multiple comparisons. All tests were 2-sided with a *P* value <0.05 considered to be significant. Analyses were conducted using SAS software for Linux, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

Characteristics of patients experiencing versus not experiencing a NCB event are shown in Table 1. As anticipated, baseline characteristics of patients differed in non-high-risk versus high-risk subgroups, which included age <65 years (plus additional risk factors), atherosclerotic manifestation in ≥2 vascular beds, renal insufficiency, heart failure, and diabetes mellitus in that patients in high-risk subgroups demonstrated a higher prevalence of risk factors and comorbidities.[7]

NCB in the Overall COMPASS Population

Significantly fewer NCB adverse outcomes were observed with rivaroxaban 2.5 mg twice a day plus ASA versus ASA alone (HR, 0.80 [95% CI, 0.70–0.91], *P*=0.0005; Figure 1, Table 2).[2] The contribution of the individual NCB components is shown in Figure 2. The main drivers of NCB outcomes were "efficacy" events, in particular stroke and cardiovascular death. In contrast, the bleeding components of the NCB, in particular fatal bleeding, only represented a small proportion of NCB events (without any significant differences between the 2 randomized groups). Sensitivity analyses counting only ST-elevation and new Q-wave MIs yielded similar results (NCB HR, 0.76 [95% CI, 0.66–0.88]; *P*=0.0002). In contrast, replacing life-threatening and fatal bleeding events with all major bleeding events according to the modified ISTH definition resulted in no detectable difference in NCB outcomes between the 2 study groups (HR, 0.99 [95% CI, 0.89–1.11], *P*=0.91) because of inclusion of a large number of less severe bleeding events.

Separation of the Kaplan-Meier curves occurred early, with a further divergence during trial progression (Figure 2A) indicating an increasing NCB with longer treatment duration (ARR per 1000 patients treated, rivaroxaban 2.5 mg twice daily plus ASA versus ASA, –3.9 [95% CI, –8.7 to 0.8], –13.9 [95% CI, –21.4 to –6.5], and –19.5 [95% CI, –28.9 to –10.0], after 12, 24, and 30 months, respectively). As such, the number of prevented "efficacy" NCB events increased, whereas the number of "safety" NCB events remained constant (and low) over time (Figure 2B).

NCB in Selected High-Risk Populations

The NCBs in selected high-risk subgroups are shown in Figure 3 and Figure 4. Kaplan-Meier curves of high-risk patients separated earlier and more markedly than for the overall population and continued to separate over time, in favor of rivaroxaban 2.5 mg twice daily plus ASA (Figure 3).

We did not observe any significant interaction in the *relative* impact of the combination of rivaroxaban plus ASA versus ASA alone in any of the high-risk subgroups. Similar HRs were observed for the respective high-risk groups, and in each instance, a lower HR was observed in the presence of the high-risk feature compared with the absence of this feature (Figure 4). In the nonprespecified subanalysis of patients ≥75 years, a directionally similar result was seen, which was, however, not significant because of the smaller sample size and resulting lack of statistical power (Table I in the Data Supplement).

Because patients in these high-risk subgroups had a substantially higher *absolute* risk, they derived a larger ARR from the combination of rivaroxaban plus ASA, and this resulted in an even lower number needed to treat (NNT). As an example, patients with estimated glomerular filtration rate <60 mL/min had a 3.8%/y event rate with rivaroxaban plus ASA as compared with 4.8% with ASA alone (HR, 0.79 [95% CI, 0.64–0.98]); in contrast, patients with estimated glomerular filtration rate ≥60 mL/min had an event rate of 2.1%/y and 2.6%/y with rivaroxaban plus ASA and ASA alone, respectively (HR, 0.81 [95% CI, 0.69–0.94], *P* interaction=0.89). The higher absolute event rate in patients with estimated glomerular filtration rate <60 mL/min led to a higher ARR (3.3% versus 1.5%) and, as a result, a lower NNT (31 versus 67 over 30 months).

The contributions of the individual components of the NCB in high-risk versus non-high-risk subgroups are shown in Table I in the Data Supplement. In line with the overall population (Figure 2, Table 2), the main

Table 1. Baseline Characteristics by Occurrence of the Net Clinical Benefit Outcome

	No NCB Event (N=17 313)	NCB Event (N=965)	*P* Value
Age, y	68.2±7.9	69.3±8.7	<0.0001
Female sex	3848 (22.2)	200 (20.7)	0.27
Body mass index, kg/m^2	28.3±4.7	28.6±5.0	0.17
Systolic blood pressure, mm Hg	136±17	138±19	<0.0001
Diastolic blood pressure, mm Hg	78±10	78±11	0.50
Total cholesterol, mmol/L	4.2±1.1	4.3±1.1	0.0004
Tobacco use			
Never	5535 (32.0)	290 (30.1)	0.21
Former	8083 (46.7)	454 (47.0)	0.83
Current	3695 (21.3)	221 (22.9)	0.25
Hypertension	12 987 (75.0)	797 (82.6)	<0.0001
Diabetes mellitus	6460 (37.3)	462 (47.9)	<0.0001
Previous stroke	621 (3.6)	65 (6.7)	<0.0001
Previous myocardial infarction	10 744 (62.1)	631 (65.4)	0.04
Heart failure	3661 (21.1)	281 (29.1)	<0.0001
Coronary artery disease	15 688 (90.6)	886 (91.8)	0.21
Peripheral arterial disease	4671 (27.0)	325 (33.7)	<0.0001
Estimated GFR			
<30 mL/min	144 (0.8)	19 (2.0)	0.0003
30 to <60 mL/min	3689 (21.3)	316 (32.7)	<0.0001
≥60 mL/min	13 476 (77.9)	630 (65.3)	<0.0001
Race			
White	10 759 (62.1)	596 (61.8)	0.81
Black	158 (0.9)	10 (1.0)	0.70
Asian	2688 (15.5)	160 (16.6)	0.38
Other	3708 (21.4)	199 (20.6)	0.56
Geographic region			
North America	2451 (14.2)	162 (16.8)	0.02
South America	3894 (22.5)	214 (22.2)	0.82
Western Europe, Israel, Australia, or South Africa	5420 (31.3)	290 (30.1)	0.41
Eastern Europe	3055 (17.6)	156 (16.2)	0.24
Asia-Pacific	2493 (14.4)	143 (14.8)	0.72
Medication			
ACE inhibitor or ARB	12 225 (70.6)	712 (73.8)	0.04
Calcium-channel blocker	4606 (26.6)	289 (29.9)	0.02
Diuretic	5107 (29.5)	366 (37.9)	<0.0001
Beta blocker	12 071 (69.7)	712 (73.8)	0.007
Lipid-lowering agent	15 567 (89.9)	830 (86.0)	0.0001
Nonsteroidal anti-inflammatory drugs	941 (5.4)	63 (6.5)	0.15
Nonstudy proton pump inhibitor	6187 (35.7)	345 (35.8)	0.99

For continuous variables, plus-minus values are mean±SD. For categorical variables, frequency (%) are shown. *P* value is from the Wilcoxon 2-sample test for continuous variables, and Pearson χ^2 test for categorical variables. ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; and NCB, net clinical benefit.

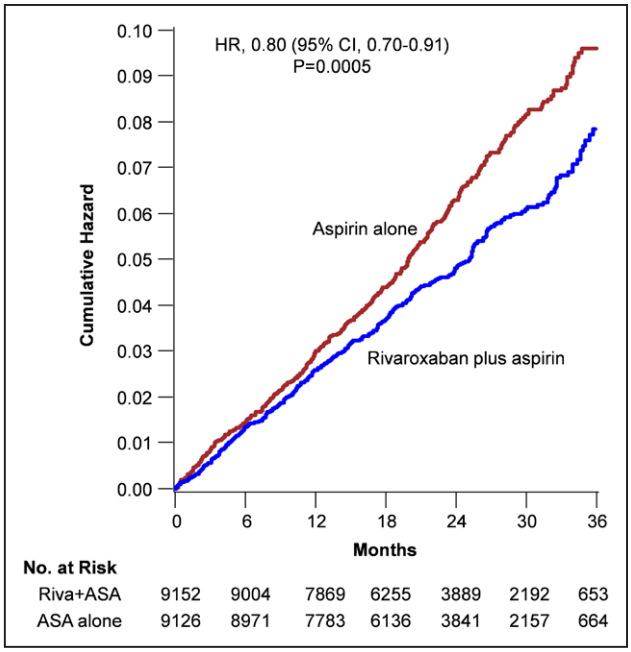

Figure 1. Cumulative incidence of the net clinical benefit outcome among participants receiving rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone.
ASA indicates acetylsalicylic acid (aspirin); HR, hazard ratio; and Riva, Rivaroxaban.

drivers of NCB outcomes were "efficacy" events, particularly in the high-risk subgroups, with lower rates for bleeding into a critical organ and markedly lower incidences in fatal bleeding.

Impact of Additional Risk Factors

The impact of additional risk factors had an additive effect in augmenting the ARR and reducing the NNT (Figure 4). When all 4 selected high-risk features were present (polyvascular, renal dysfunction, heart failure, and diabetes mellitus), an ARR of 3.37%/y and a NNT of 9 patients/30 mo was observed. For those with 3 high-risk features, the NNT at 30 months was 12, and for those with 2 high-risk features, it was 31 (Figure 4). In contrast, for those with no high-risk features, the NNT was 113.

DISCUSSION

The 4 most important findings of our analysis of the COMPASS trial are as follows:

(1) The lower rate of NCB adverse events with rivaroxaban 2.5 mg twice daily plus ASA versus ASA monotherapy was primarily driven by a reduction in "efficacy" events, whereas the increased risk in severe bleedings was markedly less frequent.

(2) The lower rate of NCB adverse events became more pronounced with increasing follow-up duration as risk of bleeding was front loaded,

Table 2. Event Rates of the Net Clinical Benefit Outcome and Its Components

	Rivaroxaban Plus Aspirin (N=9152)		Aspirin Alone (N=9126)		Rivaroxaban Plus Aspirin vs. Aspirin Alone		Absolute Risk* Reduction (95% CI), Events Prevented/ Caused, per 1000 Patients at 30 mo	NNT*/ NNH
	No. of First Events/ Patients (%)	Annual Rate, %/y	No. of First Events/Patients (%)	Annual Rate, %/y	Hazard Ratio (95% CI)	*P* Value		
Net clinical benefit outcome	431/9152 (4.7)	2.5	534/9126 (5.9)	3.1	0.80 (0.70–0.91)	0.0005	–19.5 (–28.9 to –10.0)	52
Cardiovascular death	160/9152 (1.7)	0.9	203/9126 (2.2)	1.2	0.78 (0.64–0.96)	0.02	–8.2 (–14.2 to –2.2)	122
Stroke	83/9152 (0.9)	0.5	142/9126 (1.6)	0.8	0.58 (0.44–0.76)	<0.0001	–10.6 (–15.6 to –5.6)	95
Myocardial infarction	178/9152 (1.9)	1.0	205/9126 (2.2)	1.2	0.86 (0.70–1.05)	0.14	–4.8 (–10.8 to 1.2)	209
Fatal bleeding	15/9152 (0.2)	0.09	10/9126 (0.1)	0.06	1.49 (0.67–3.33)	0.32	0.4 (–1.5 to 2.2)	2671
Symptomatic bleeding into critical organ	73/9152 (0.8)	0.4	53/9126 (0.6)	0.3	1.37 (0.96–1.95)	0.08	2.8 (–0.8 to 6.3)	362

Percent (%) is the proportion of patients with an outcome. Percent per year (%/y) is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event. Hazard ratios (95% CI) are from the stratified Cox proportional hazards regression models fit in the respective subgroup. *P* values are from the stratified log-rank test. NNH indicates number needed to harm; and NNT, number needed to treat.

*Based on Kaplan-Meier estimates of cumulative risk at 30 mo.

whereas benefits in terms of reduction of cardiovascular disease events accrued throughout the treatment periods.

(3) A higher ARR for NCB adverse outcomes was observed in the investigated high-risk subgroups, resulting in an even lower NNT.

(4) Combining risk characteristics increased the ARR and increased the NCB.

NCB Analysis in COMPASS

Patients with "stable" coronary artery disease or PAD remain at a substantially increased long-term risk of cardiovascular events.[1] In the current European Society of Cardiology Guidelines, patients formerly termed to have "stable" coronary artery disease are now referred to as having "chronic coronary syndromes," reflecting that these individuals are only stable in relative terms (compared with immediately following an acute events such as MI) but remain at an increased risk of cardiovascular events over time.[1] As such, prolonging an intensified anticoagulant regimen (such as by adding rivaroxaban 2.5 mg twice daily to low-dose ASA) has been given a class IIa and IIb indication for patients at severe and moderate risk of recurrent events, respectively.[1] Indeed, the addition of rivaroxaban 2.5 mg twice daily to ASA monotherapy has been shown in the COMPASS trial to reduce the risk of the composite of MI, stroke, and cardiovascular death by 24%. Conversely, however, a 70% relative increase in the broad definition of "major bleeding" events was observed. In consequence, there is the perception that the risks of adding rivaroxaban 2.5 mg twice daily may counterweigh the benefits. To put these findings into context, a more detailed analysis is required as a more inclusive definition of major bleeding was used in COMPASS than in other trials of antithrombotic therapy. The ISTH major bleeding definition (fatal bleeding, symptomatic bleeding into a critical area or organ, bleeding causing a decrease in the hemoglobin level of ≥2 g/dL, or bleeding that led to transfusion of ≥2 U of whole blood or red cells) was adapted for the COMPASS trial in response to regulators' requests so that the modified ISTH definition also included any bleeding that resulted in hospitalization (with or without overnight stay), and did not require a drop in hemoglobin or transfusion. As such, major bleeding rates were about one-third more frequent than with the original ISTH definition, and many "major" bleedings occurring in COMPASS would not have been considered "major" bleedings in other large outcome trials.[8] This is of critical importance as the main driver of the 70% increase in major bleeding observed in the trial were bleedings that led to presentation to an acute care facility or hospitalization,[2,8] whereas the incidence of more severe bleeding events (ie, fatal or nonfatal symptomatic bleedings into critical organs) was low and not different between the 2 treatment arms. A "top-line" comparison of the reduction in the composite primary efficacy end point versus the increase in the principal safety end point therefore has many important shortcomings mainly related to the mismatch in the clinical significance of included efficacy and bleeding events.

The predefined NCB offers 2 important advantages over separate assessment of efficacy and safety end points. First, it only encompasses the most severe "efficacy" and "safety" events (ie, MI, stroke, and cardiovascular death as well as fatal bleeding and symptomatic bleeding into a critical organ). As a result, NCB rates are not diluted by events of lesser severity but instead represent a selection of outcomes with serious clinical consequences. Second, the inclusion of these events into *1* composite outcome ensures that each patient is only counted once even if they have multiple events and also allows for an easy and comprehensive assessment

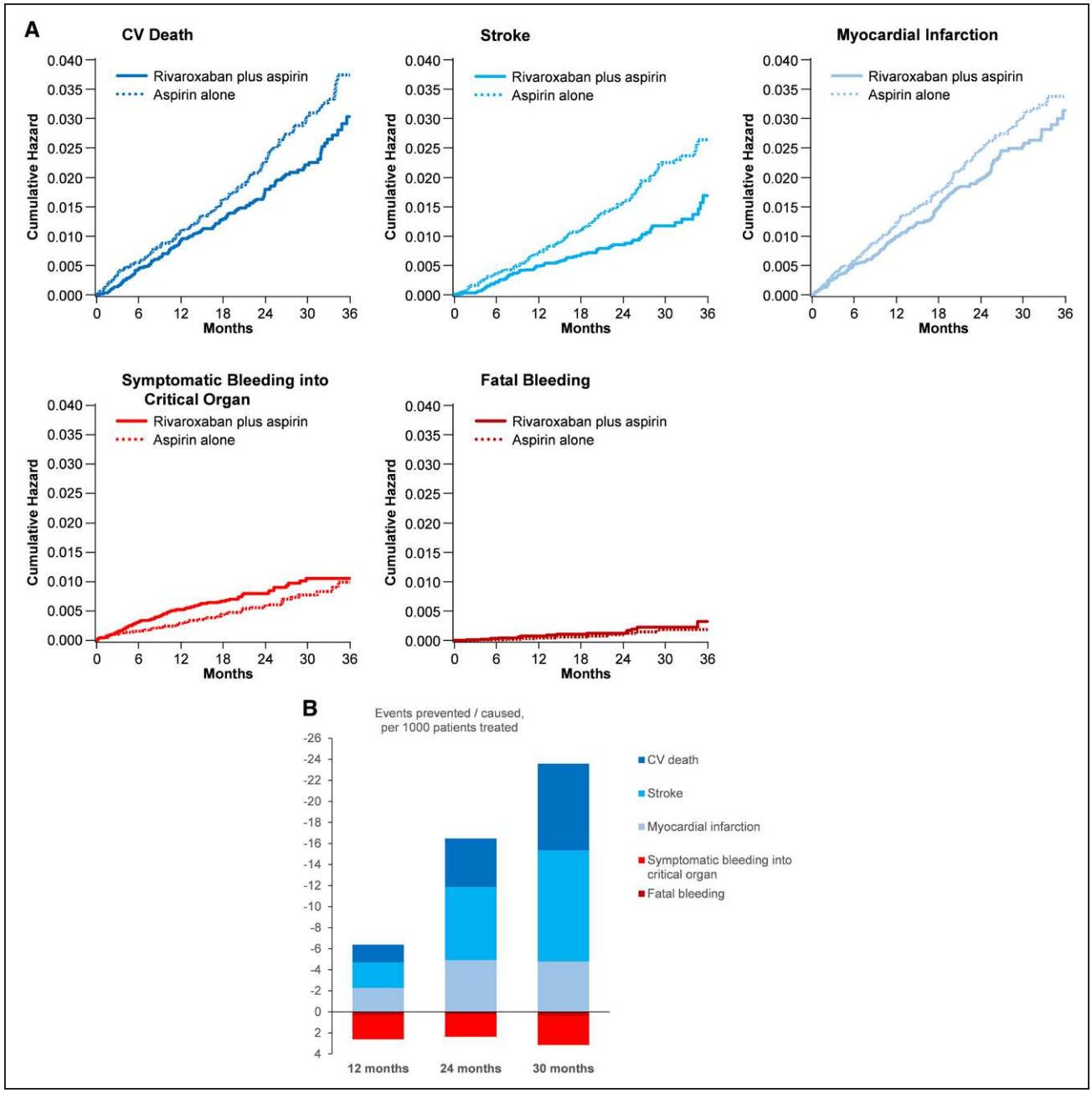

Figure 2. Incidence of the net clinical benefit outcome components.
A, Cumulative incidence of the net clinical benefit outcome components among participants receiving rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone. **B**, Net clinical benefit events prevented/caused per 1000 patients treated with rivaroxaban 2.5 mg twice daily plus aspirin vs aspirin alone. CV indicates cardiovascular.

of the overall benefit of the new treatment regimen rather than having to separately compare event rates and HRs of several different end points. Although any bleeding event may have an impact on subsequent events, "symptomatic bleeding into a critical organ" was included in the NCB because such life-threatening bleedings have been associated with a >3-fold larger increase in mortality than "major bleedings."[9] In contrast, the increase in modified ISTH major bleeding events in COMPASS meant that the majority of those bleeding events were neither fatal nor involved bleeding into a critical organ. This conclusion is strengthened by the 18% reduction in all-cause mortality of rivaroxaban 2.5 mg twice daily plus ASA over ASA monotherapy observed in the overall trial.[2]

Contribution of Severe Ischemic and Bleeding Events to the NCB

Our current analysis indicates that the trial "efficacy" outcomes constituted the majority of events factoring into the NCB composite. In this analysis of bleeding

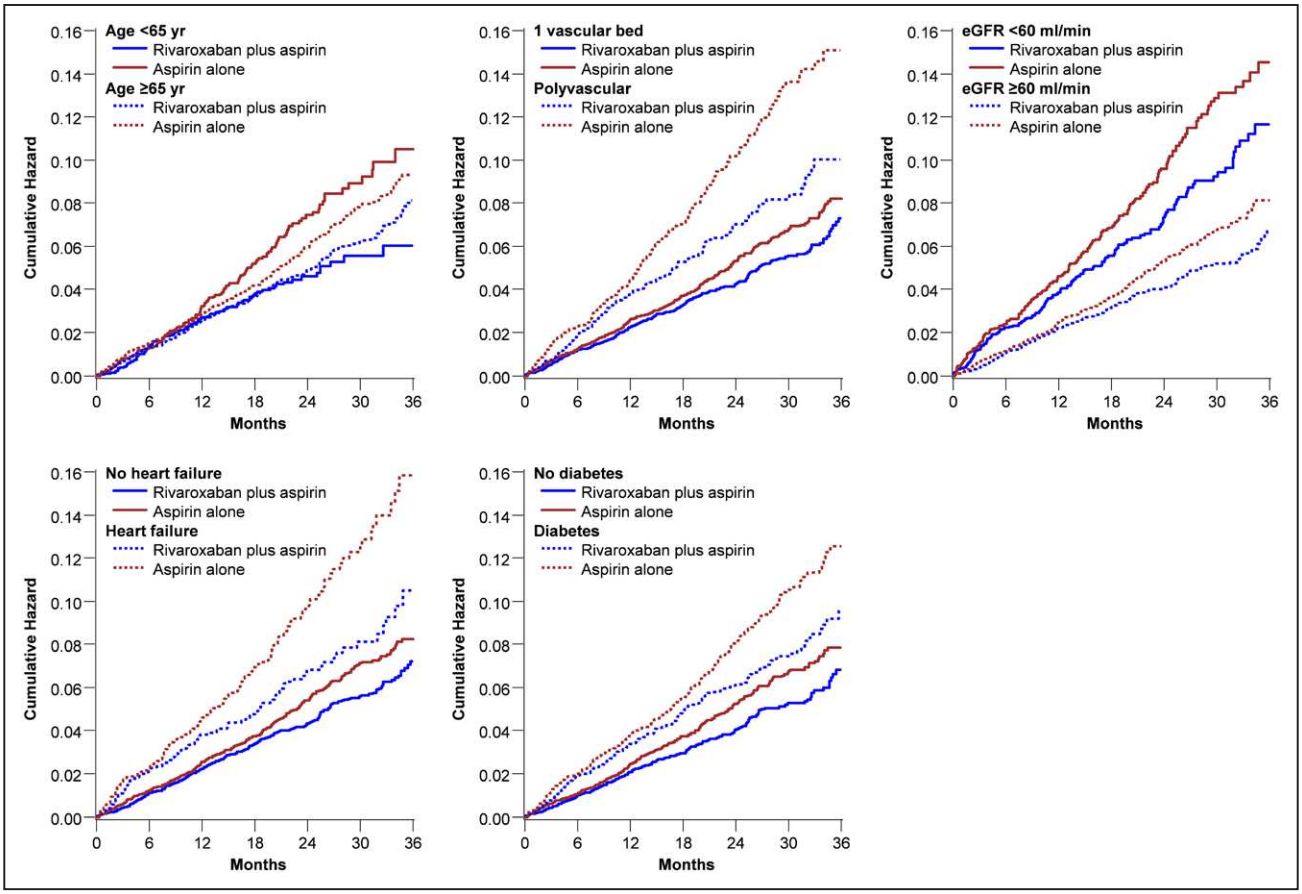

Figure 3. Cumulative incidence of the net clinical benefit outcome according to selected risk characteristics in participants receiving rivaroxaban 2.5 mg twice daily plus aspirin or aspirin alone.
eGFR indicates estimated glomerular filtration rate.

events with the most important clinical impact (fatal or bleeding into a critical organ), the absolute event rates were lower and mostly not statistically different between the 2 treatment arms. As a result, the larger reduction of severe ischemic outcomes outweighed the increase in severe bleeding events.

Time Course of Events Contributing to NCB

The antithrombotic comparisons in the COMPASS trial were discontinued early on the advice of the data and safety monitoring board because of the finding of >4

Subgroup	Rivaroxaban plus Aspirin		Aspirin Alone		Hazard Ratio with Rivaroxaban plus Aspirin (95% CI)	P Value for Interaction	NNT
	No. of events / patients	*%/yr*					
Overall	431 / 9152	2.5	534 / 9126	3.1	0.80 (0.70-0.91)		52
Age						0.13	
<65 yr	88 / 2150	2.4	134 / 2184	3.6	0.67 (0.51-0.87)		32
≥65 yr	343 / 7002	2.5	400 / 6942	3	0.84 (0.73-0.97)		63
Vascular beds						0.16	
1	309 / 7246	2.2	360 / 7239	2.6	0.85 (0.73-0.99)		86
≥2	122 / 1906	3.5	174 / 1887	5	0.69 (0.55-0.87)		21
eGFR						0.89	
<60 ml/min	147 / 2054	3.8	188 / 2114	4.8	0.79 (0.64-0.98)		31
≥60 ml/min	284 / 7094	2.1	346 / 7012	2.6	0.81 (0.69-0.94)		67
Heart failure						0.15	
No	315 / 7189	2.3	369 / 7147	2.7	0.85 (0.73-0.99)		69
Yes	116 / 1963	3.4	165 / 1979	4.9	0.69 (0.55-0.88)		25
Diabetes						0.78	
No	227 / 5704	2.1	276 / 5652	2.6	0.81 (0.68-0.97)		71
Yes	204 / 3448	3.1	258 / 3474	4	0.78 (0.65-0.94)		36
Polyvascular, renal dysfunction, heart failure, diabetes						0.21	
None or 1 out of 4	252 / 6612	2	283 / 6553	2.3	0.88 (0.74-1.04)		113
2 out of 4	129 / 1936	3.6	164 / 1941	4.7	0.78 (0.62-0.98)		31
3 out of 4	43 / 548	4.4	75 / 557	7.7	0.56 (0.38-0.81)		12
4 out of 4	7 / 56	7	12 / 75	10.3	0.71 (0.28-1.83)		9

Figure 4. Event rates of net clinical benefit outcome in selected high-risk subgroups.
eGFR indicates estimated glomerular filtration rate; and NNT, number needed to treat.

SDs of benefit in the primary efficacy outcome for rivaroxaban 2.5 mg twice daily plus ASA versus ASA.[2] However, the time course of safety and efficacy events differed.[8] The excess in major bleeding events was confined to the first year, whereas the benefits in efficacy events continued to separate over time.[8] An increased bleeding risk early during initiation of anticoagulant or antiplatelet therapy is not uncommon and can be related to an unmasking of a causal pathology.[10–12] In contrast, the reduction in efficacy events was augmented over time, resulting in an increasingly favorable NCB for the combination of rivaroxaban 2.5 mg twice daily plus ASA.[7] Thus, the early discontinuation of the trial underestimated the NCB over the longer term because of the weighting of bleeding events in the first year of the trial. This is of relevant clinical importance, particularly for long-term and potentially lifelong treatment regimens such as those for chronic coronary syndromes or PAD.

NCB in High-Risk Populations

Selected high-risk patient populations derived a statistically similar NCB from the combination of rivaroxaban 2.5 mg twice daily as compared with ASA monotherapy in relative terms, and this resulted in a higher ARR and an even lower NNT. As for the overall population, this benefit was primarily driven by a reduction in efficacy events. These results are of particular importance as rivaroxaban 2.5 mg twice daily plus ASA has the largest clinical benefit in patients with combinations of high-risk features. Such patients may currently be excluded from additional antithrombotic therapies based on clinical overestimation of bleeding risks and the lack of clear evidence of NCB.

At the same time, however, although ischemic event rates were lower in lower-risk patients, also these individuals are at considerable residual risk and should benefit from the combination of rivaroxaban 2.5 mg twice daily and ASA over the midterm to longer term. Indeed, also in these patients, the NCB became more favorable over time.

Limitations

Patients at sufficiently high risk of bleeding to preclude more intensive antithrombotic therapy were excluded from the COMPASS trial; as such, our findings cannot be extrapolated to patients with an exclusion for antithrombotic therapy. This analysis of NCB may underestimate potential longer-term benefits of this therapy because the early termination of the COMPASS trial results in greater weighting of early bleeding events in the analysis of NCB.

Conclusions

The lower rate in NCB adverse events through the addition of rivaroxaban 2.5 mg twice daily to ASA was primarily driven by a reduction in severe efficacy events, particularly stroke and cardiovascular mortality, whereas severe bleeding events were less frequent and had less impact. The excess in major and severe bleeding events was mainly confined to the first year of treatment in the trial. The NCB was increasingly favorable with increasing study duration, and even more pronounced in high-risk patient subgroups, particularly with combinations of risk characteristics. The NCB of rivaroxaban 2.5 mg twice daily plus ASA may hence represent an easy-to-use metric to comprehensively estimate the overall benefit of this treatment regimen in patients with chronic coronary syndromes and/or peripheral artery disease.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Table I

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